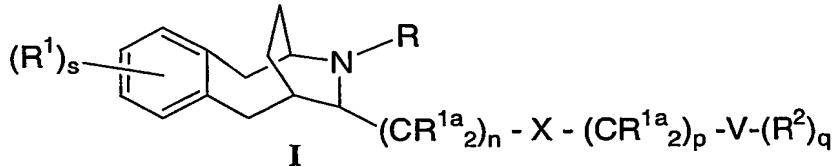


WHAT IS CLAIMED IS:

1. A compound of Formula I



5 wherein

R is selected from

- 1) H,
- 2) OR⁴,
- 3) unsubstituted or substituted C₁-C₁₀ alkyl,
- 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 6) unsubstituted or substituted heterocycle,
- 7) -C(O)R⁴,
- 8) C(O)OR⁴, and
- 15 9) C(O)N(R⁴)₂;

R^{1a} is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₆ alkyl, and
- 20 3) OR⁴;

R^{1b} is independently selected from

- 1) H, and
- 2) unsubstituted or substituted C₁-C₆ alkyl;

25

X is selected from

- 1) a bond,

- 2) C(O),
- 3) O, and
- 4) NR⁴;

5 R¹ is independently selected from

- 1) H,
- 2) halo,
- 3) OR⁴,
- 4) NO₂,
- 10 5) -S(O)_mR⁴,
- 6) CN
- 7) unsubstituted or substituted C₁-C₁₀ alkyl,
- 8) unsubstituted or substituted aryl,
- 9) unsubstituted or substituted C₂-C₆ alkenyl,
- 15 10) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 11) unsubstituted or substituted alkynyl,
- 12) unsubstituted or substituted heterocycle,
- 13) -C(O)R⁴,
- 14) C(O)OR⁴,
- 20 15) C(O)N(R⁴)₂,
- 16) S(O)_mN(R⁴)₂, and
- 17) N(R⁴)₂;

V is selected from

- 25 1) H,
- 2) CF₃,
- 3) aryl,
- 4) heterocycle, and

5) C₃-C₁₀ cycloalkyl;

R² is independently selected from

- 1) H,
- 5) 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) -(CR^{1b})_tOR⁴,
- 4) Halo,
- 5) CN,
- 6) NO₂,
- 10) 7) CF₃,
- 8) -(CR^{1b})_tN(R⁴)₂,
- 9) -C(O)OR⁴,
- 10) 10) -C(O)R⁴,
- 11) 11) -S(O)₂R⁴,
- 15) 12) -(CR^{1b})_tNR⁴(CR^{1b})_tR⁵,
- 13) 13) -(CR^{1b})_tS(O)_mNR⁴,
- 14) 14) -C(O)OR⁴R⁵,
- 15) 15) -NR⁴C(O)R⁴,
- 16) 16) unsubstituted or substituted aryl, and
- 20) 17) 17) unsubstituted or substituted heterocycle;

R⁴ is independently selected from

- 1) H,
- 2) 25) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 4) 4) unsubstituted or substituted aryl,
- 5) 5) unsubstituted or substituted heterocycle, and
- 6) 6) CF₃;

R⁵ is independently selected from

- 1) unsubstituted or substituted aryl, and
- 2) unsubstituted or substituted heterocycle;

5 m is independently 0, 1 or 2;

n is 0 to 6;

p is 0 to 6;

q is 0 to 6, provided that when V is H or CF₃, q is 0; and

s is 0 to 16;

10 t is independently 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. The compound according to Claim 1 wherein R^{1b}, R⁴, R⁵ and
15 variables m, n, p, q and t are as defined in Claim 1 and

R is selected from

- 1) H,
- 2) OR⁴,
- 20 3) unsubstituted or substituted C₁-C₁₀ alkyl, and
- 4) unsubstituted or substituted aryl.

R^{1a} is independently selected from

- 1) H, and
- 25 2) unsubstituted or substituted C₁-C₆ alkyl;

X is selected from

- 1) a bond, and
- 2) C(O);

30

R^1 is independently selected from

- 1) H,
- 2) halo,
- 3) OR^4 ,
- 5) $N(R^4)_2$,
- 5) NO_2 , and
- 6) unsubstituted or substituted C_1-C_{10} alkyl;

V is selected from

- 10 1) H,
- 2) CF_3 ,
- 3) aryl, and
- 4) heterocycle;

15 R^2 is independently selected from

- 1) H,
- 2) unsubstituted or substituted C_1-C_{10} alkyl,
- 3) $-(CR^{1b})_tOR^4$,
- 4) Halo,
- 20 5) CN ,
- 6) NO_2 ,
- 7) CF_3 ,
- 8) $-(CR^{1b})_tN(R^4)_2$,
- 9) $-C(O)OR^4$,
- 25 10) $-(CR^{1b})_tS(O)_mNR^4$,
- 11) $-(CR^{1b})_tNR^4(CR^{1b})_tR^5$,
- 12) $-C(O)OR^4R^5$, and
- 13) $-NR^4C(O)R^4$;

s is 0 to 6;
or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound according to Claim 1 wherein R^{1b}, X, R¹, R²,
5 R⁴, R⁵ and variables m and t are as defined above and:

R^{1a} is independently selected from

- 1) H, and
- 2) unsubstituted or substituted C₁-C₆ alkyl;

10

V is selected from

- 1) aryl, and
- 2) heterocycle;

15 n is 0 to 3;

p is 0 to 3;

q is 0 to 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

20

4. A compound that is:

(6R,9S,11R)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[a][8]annulene;

25 (6R,9R,11S)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[a][8]annulene;

(6S,9R,11R)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[a][8]annulene;

30

(6S,9R,11S)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[a][8]annulene;

(6*S*,9*R*,11*S*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[*a*][8]annulene;

5 (6*S*,9*R*,11*R*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[*a*][8]annulene;

(6*R*,9*S*,11*S*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[*a*][8]annulene;

10 (6*R*,9*S*,11*R*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo
[*a*][8]annulene;

(6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)
benzo[*a*][8]annulene;

15 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)
benzo[*a*][8]annulene;

20 (6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)
benzo[*a*][8]annulene;

(6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)
benzo[*a*][8]annulene;

25 (6*S*,9*R*,11*S*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(
epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*R*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(
epiminomethano)benzo[*a*][8]annulene;

30 (6*R*,9*S*,11*S*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(
epiminomethano)benzo[*a*][8]annulene;

35 (6*R*,9*S*,11*R*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(
epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;

5 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;

(6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;

10 (6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;

(6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;

15 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;

20 (6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;

(6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;

25 (6*S*,9*R*,11*S*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*R*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

30 (6*R*,9*S*,11*S*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

35 (6*R*,9*S*,11*R*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*S*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

5 (6*S*,9*R*,11*R*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*,11*S*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

10 (6*R*,9*S*,11*R*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*S*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

15 (6*S*,9*R*,11*R*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*,11*S*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

20 (6*R*,9*S*,11*R*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*R*,9*S*,11*R*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

25 or a pharmaceutically acceptable salt or stereoisomer thereof.

5. A compound according to Claim 4 that is:

(6*R*,9*S*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

30 (6*R*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

(6*S*,9*R*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;

35

(6*S*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo [a][8]annulene;

or a pharmaceutically acceptable salt or stereoisomer thereof.

5

6. A pharmaceutical composition which is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

10 7. A method of modulating the catalytic activity of protein kinases in a mammal in need thereof comprising contacting the protein kinase with a compound of Claim 1.

15 8. The method of Claim 7 wherein the protein kinase is an RTK.

15 9. The method of Claim 8, wherein the RTK is selected from IR, IGF-1R and IRR.

20 10. A method of treating or preventing a PK-related disorder in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Claim 1.

11. A method of Claim 10, wherein the PK-related disorder is an IGF-1R-related disorder selected from:

25 1) cancer,
2) diabetes,
3) an autoimmune disorder,
4) a hyperproliferation disorder,
5) aging,
6) acromegaly, and
30 7) Crohn's disease.

12. A method of treating cancer in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of Claim 1.

5 13. A method of treating retinal vascularization comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compoung of Claim 1.

10 14. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a second compound selected from:

15 1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
20 9) a reverse transcriptase inhibitor, and
10) an angiogenesis inhibitor.

15. The method of Claim 14, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

25

16. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

17. The method of Claim 16 wherein radiation therapy is also administered.

18. A method of treating cancer which comprises administering a 5 therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.

19. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a 10 GPIIb/IIIa antagonist.

20. The method of Claim 19 wherein the GPIIb/IIIa antagonist is tirofiban.

15 21. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.